The T wave: physiology and pathophysiology
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Chapter 8

Summary and future perspectives
THE T WAVE: PHYSIOLOGY AND PATHOPHYSIOLOGY

The T wave on the electrocardiogram (ECG) represent the repolarization of the ventricular myocardium. Abnormalities in repolarization and abnormal T waves are related with a higher risk for life-threatening arrhythmias. However, a thorough understanding of the T wave in relation with the underlying repolarization pattern is lacking. The aim of this thesis was to elucidate some aspects of the physiology and pathophysiology underlying the T wave and to explore the effects of various factors (pressure, drugs, autonomic nervous system, positional changes) on the morphology of the T wave.

PHYSIOLOGY UNDERLYING THE T WAVE

We show in Chapter 2 that, even for the normal T wave, there is a hiatus in the relation between T wave morphology and the corresponding repolarization pattern. We provide the first complete correlation between local repolarization and the corresponding electrocardiographic T wave. Repolarization heterogeneity in the entire heart, rather than the heterogeneity along a single anatomic axis is determinative for the T wave.

The novelty in this chapter is that it demonstrates that repolarization is a nonlinear process in which at the moment of the peak of the T wave only 25% of ventricular sites is repolarized. From these results we infer that the first part of the normal T wave primarily depends on differences in action potential morphology (i.e. due to phase 1 and 2 of the action potential). Accordingly, the last part of the T wave is mainly explained by differences in the steepest part of repolarization (phase 3). We speculate that abnormalities in the part of the T wave following the peak may indicate relevant changes in heterogeneity in the end of repolarization, which have implication on the vulnerability for arrhythmias. Indeed a prolonged Tpeak-to-Tend interval has been associated with sudden cardiac death. On the other hand, we realize that repolarization heterogeneity is not the only prerequisite to initiate re-entry.

The normal T wave has a longer onset-to-peak duration than peak-to-end duration. Based on our results we infer that it represents a longer interval of differences in the action potential (AP) plateau phase than of differences in full repolarization moments. The symmetry of the T wave may therefore reveal information about the course of the AP plateau. We speculate that when the AP morphology starts to resemble a block pulse morphology, the interval in which AP plateau differences occur becomes shorter, whereas the interval in which differences in full repolarization occur will remain unchanged. This may result in a symmetric T wave. Indeed during hyperkalemia phase 3 of the AP is steeper and symmetric T waves are present.
Although the results were obtained from pig hearts, the activation and repolarization patterns and the T wave resemble those described in humans considerably.\textsuperscript{8,9,10} Nevertheless, in order to affirm that the mechanism proposed in this thesis holds for T waves in humans, experiments needs to be repeated in human hearts.

**MODULATION BY LEFT VENTRICULAR PRESSURE**

Stretch influences the action potential duration and plays a relevant role in arrhythmogenesis.\textsuperscript{11} This modulation is known as mechano-electric coupling (MEC) and results from the activation of stretch-activated channels in the cell membrane.\textsuperscript{12} Since many studies have focused on the stretch effect in diseased conditions, we were interested in the MEC effect of physiologic pressures within the normal heart. Chapter 3 presents the results of the influence of physiologic left ventricular (LV) pressure on repolarization and action potential duration. The novelty of this study is that we stimulated from either the LV free wall or septum in order to change the timing of activation (and thus repolarization) with respect to the pressure pulse, without altering the myocardial substrate (i.e. electrical and mechanical properties). Results in this chapter demonstrates that the presence of LV pressure synchronizes repolarization in the heart, by prolonging the repolarization of intrinsically early repolarizing cardiomyocytes more than the intrinsically late repolarizing cardiomyocytes. The latter may even show shortening of the repolarization when the cycle length is short. These results implicate that systolic pressures – within the physiological range – reduce heterogeneity in repolarization via mechano-electric coupling. We suggest that this will narrow the T wave (see Figure 1) and may protect the heart against arrhythmias. In the absence of LV pressure, repolarization is shorter and dispersion in repolarization is larger, which are both critical conditions for the initiation of re-entry.\textsuperscript{13} Systolic pressure is commonly low during a short-coupled premature beat and may therefore – via mechano-electric coupling – broaden the T wave and increase the vulnerability for arrhythmias, especially in the already compromised heart. This implies that a second premature beat is more arrhythmogenic than a first premature beat. Janse et al have tested the assumption that a second premature beat is associated with more heterogeneity in refractory periods.\textsuperscript{14} This was not the case, but these experiments were executed in Langendorff perfused porcine hearts, where left ventricular pressure is absent. Timing of the pressure pulse with regards to the moment of repolarization is also important in the extent of prolongation of repolarization. This may be relevant in diseases with a potentially shifted timing of the pressure pulse with respect to the repolarization moment.

The majority of studies in literature only describes MEC effects on action potential duration and repolarization, but it is also relevant to know how the stretch-induced changes
in repolarization are translated to the ECG. **Chapter 4** describes the impact of LV pressure on the STT segment of the ECG and on the underlying repolarization. The results demonstrated that increase in LV pressure causes little prolongation of repolarization in the LV, but no prolongation in the RV, resulting in larger interventricular dispersion in RT. This led to large increases in the amplitudes of the STT integrals and QT intervals without changing the pattern of the STT integral maps. Prolongation of the QT interval was larger than prolongation of the repolarization. This discrepancy implies that the increase in pressure changes primarily the morphology at the end of the action potential, which is consistent with the AP prolongation resembling an afterdepolarization as described by Franz et al.\textsuperscript{15} We conclude that increased diastolic pressure leads to concomitant rise in systolic pressure and results in a small prolongation of repolarization times. In addition, a slightly larger prolongation of the QT intervals and increases in the amplitude of the STT segment on the ECG occurs (see Figure 1).
Considering both studies on LV pressure effects, I suggest that the T wave morphology may be of added value in cardiac resynchronization therapy (CRT). In patients with heart failure, CRT is focused on synchronizing the contraction of the heart in order to increase the ejection fraction. The synchronization may, however, result in extreme strain patterns within the heart that unintentionally increase the vulnerability for arrhythmias. The T wave morphology may be indicative for these extreme strain patterns and consequently predicting the risk for arrhythmias. CRT has already been shown to induce arrhythmias. Also, an increased Tpeak-to-Tend interval was shown to be an independent predictor of appropriate ICD therapy. A detailed analysis of the relation between T wave morphology and strain patterns within heart failure patients is needed to determine its predictive value for arrhythmias. In this exploration the activation sequence should also be incorporated as this influences the T wave morphology considerably.

**PATHOPHYSIOLOGY UNDERLYING THE T WAVE**

In this thesis we have discussed some ECG abnormalities related to abnormal repolarization. In Chapter 5 we try to unravel the mechanism underlying inferolateral J-waves. In the literature there is controversy whether the mechanism underlying the genesis of inferolateral J-waves is based on depolarization or repolarization. The results of this chapter provide important support for the depolarization hypothesis, because we demonstrate that conduction slowing in the LV lateral region can induce J-waves on the ECG. In the same model a regional increase in transient outward current is less provocative. However, our data do not completely exclude the role of early repolarization or a combination of conduction and repolarization changes. We have also tested tissue conductivity as a contributor to J-waves. A reduced tissue conductivity – e.g. due to cellular uncoupling – results in a lower current generated by the activation wave front and will cause a smaller potential field on the torso. Diffuse fibrosis causes conduction slowing and should therefore be able to induce J-waves. However, the concomitant reduction in tissue conductivity reduces the likeliness of inducing J-waves. Based on these results we suggest that conduction slowing can induce inferolateral J-waves and that its genesis may depend on tissue conductivity, size and location of the region within the heart that is involved. The model did not provide an explanation for arrhythmogenesis in the presence of J-waves caused by conduction slowing. Conduction slowing is one of the requirements for the initiation of re-entry. Therefore it is not unlikely that the regional conduction slowing may facilitate re-entry.

The thesis also provides insights in the electrocardiographic abnormalities in long QT syndrome (LQTS). Chapter 6 presents an explanation for the bifid morphology of the
T wave in type 2 LQTS. An increased interventricular dispersion of repolarization induces bifid T waves on the ECG, with earlier repolarization in the right ventricle and later repolarization in the left ventricle. Although the data were obtained from a dog model with a drug-induced LQT2 syndrome, we have arguments that suggest a similar mechanism in human. Firstly, the bifid T wave morphology is typical for both congenital and acquired LQTS in human. Besides, the configuration of the bifid T wave peaks observed in humans (i.e. larger first T wave peak in right precordial leads and larger second T wave peak in left precordial leads) corresponds with our suggestion that the first peak of the bifid T wave reflects (earlier) repolarization of the RV and that the second peak of the bifid T wave reflects (later) repolarization of the LV. We also showed in this chapter that the width of the T wave – as surrogate for the time interval between bifid T wave peaks – is highly correlated with the interventricular dispersion in repolarization. It would be of great interest to investigate whether the time interval between the bifid T wave peaks may also be correlated with the risk for arrhythmias in a clinical study.

Chapter 7 describes the beat-to-beat response of the QT and TQ (= diastolic interval on ECG) intervals to rapid stand-up in LQT1 and LQT2 patients and controls. We demonstrate a transient and large TQ shortening in response to an increase in heart rate, which was not different between LQT patients and controls. The gradual and smaller response in QT differs between groups, with QT shortening in the controls more than in LQT1 patients and with minor QT shortening or even prolongation in LQT2 patients. As a direct consequence, QTc intervals become suddenly longer (QT-stretching) in all groups in the first period after standing. I argue that QT-stretching is a poor denomination of the physiological consequence of standing up from a recumbent position, because it represents a lack of immediate adaptation of the QT interval to the change in heart rate rather than an abnormal prolongation of the QT interval. Viskin et al also commented on this point in an earlier study.

We describe that the period following the acute TQ shortening may be more discriminative between groups. Based on these results we propose that the QT/TQ-crossover metric, or several QT and TQ values, during a supine-standing test may be of potential added discriminative value for the diagnosis of LQTS, especially in patients with a normal QTc at rest. We should, however, be cautious in applying this metric directly to the clinic, because individuals in our study groups were not selected on the basis of a normal QTc value at baseline. With this study we would like to express our concerns about the use of QTc values in dynamic conditions, as the QTc is typically based on steady-state conditions.

Chapter 7 also presents differences in restitution lines between LQT patients and controls. We conclude that the restitution slopes are steeper in LQT1 patients compared to LQT2 patients and controls. A restitution slope larger than 1 has been associated with
an increased risk for ventricular arrhythmias. Coronel et al showed, however, that the critical value of 1 for the restitution slope is not required to induce re-entry. The combination of conduction delay and the restitution characteristics of the earlier repolarizing tissue is critical for the initiation of re-entry. This implies that also for LQT patients an increased restitution slope in itself would only be arrhythmogenic when also a certain activation delay occurs.

**TRANSMURALITY AND THE T WAVE**

Many cardiology textbooks describe the T wave as the result of transmural dispersion of repolarization with the epicardial layers repolarizing earlier than the endocardial layer. In this thesis we demonstrate that in an intact heart transmural dispersion of repolarization is small and only plays a minor role in the genesis of the T wave. Previously, others have examined the role of transmurality, and also concluded that transmural dispersion in repolarization and action potential duration in the intact heart is small. Accordingly, they suggested that it would contribute little to the origin of the T wave. We recorded repolarization gradients throughout the entire heart simultaneously with the T wave on an ECG and the results confirm this suggestion. Therefore, I propose that textbooks need to be reviewed concerning the description of the T wave genesis and it should be considered to incorporate insights inferred from this thesis.

**IMPLICATIONS FOR THE T WAVE MORPHOLOGY**

Figure 1 presents a summarizing representation of the physiology and pathophysiology underlying the T wave derived from the studies presented in this thesis. The figure shows a normal T wave (solid black line), with a longer onset-to-peak interval than a peak-to-end interval. The former interval (light grey area) is mainly created by differences in action potential shape (ΔAP) and in less extent by differences in full repolarization moments (ΔRT). The Tpeak-to-Tend interval (dark grey area) is mainly the result of differences in the full repolarization moments of the majority (about 75%) of the heart.

Pressure can modulate the T wave. Loss of a relevant systolic LV pressure (Psys LV) will generate more heterogeneous repolarization within the heart resulting in a wider T wave (light green area). An increase in diastolic LV pressure (Pdias LV) will mainly influence the end of the action potential morphology leading to little prolongation of the repolarization. This will result in longer QT intervals (due to a longer ‘tail’) and a larger T wave amplitude (dark green area).
Conduction slowing – e.g. as result of a reduced sodium conductivity \( G_{Na} \) – in the LV lateral region of the heart may induce J-waves (notch or slur) in the inferolateral leads of an ECG (blue line). The J-wave amplitude will depend on the tissue conductivity within the heart, in which a lower tissue conductivity may reduce the amplitude.

Interventricular dispersion in repolarization in the heart contributes to a bifid morphology of the T wave. A loss of \( I_{Kr} \) – in LQT2 patients – may lead to an increased interventricular dispersion in repolarization \( dRT_{inter} \), which results in a bifid T wave (red line). The first peak of the bifid T wave will be generated by repolarization in the RV and the second peak will be generated by repolarization in the LV.

In LQT patients the dynamics in QT in response to an increase in heart rate is impaired. In the normal heart (black striped line) shortening of the TQ interval (i.e. diastolic interval on the ECG) will cause an appropriate QT shortening. With a similar shortening of the TQ interval, LQT1 patients have a moderate QT shortening (black dot-striped line) and LQT2 patients have a minor QT shortening and may even show minor QT prolongation (black dotted line). The differences in T wave morphology between LQT1 and LQT2 were not incorporated in the figure.
REFERENCES


